REMARKS

Upon entry of the amendments herein, claims 2-9, 11-17, 19-23, 25, 26, 28-33, 41, 42, 47, 54 and 61 remain pending in the application. However, claims 3, 9, 11-17, 19-23, 25, 26, 28-33, 47, 54 and 61 remain withdrawn due to a restriction requirement, and only claims 2, 4-8, 41 and 42 are currently being considered by the Examiner. It is anticipated that, upon agreement as to allowable subject matter in the claims currently being considered, at least some of the withdrawn subject matter, particularly that connected with methods of treatment, will be rejoined to that presently being considered.

Of the claims presently being considered, claim 2 has been amended herein in the interest of more clearly and particularly reciting the subject matter regarded as the invention. Although claim 3 stands among the claims that presently remain withdrawn, it has also been amended herein; the definition of substituent R_7 in claim 3 has been amended in the same way as corresponding substituent R_1 has been amended in claim 2. Support for this amendment can be found on page 12, lines 17-29 and page 14, lines 1-6 of the instant specification. No new matter has been introduced by any of the amendments herein.

Claims 2, 4, 5, 8, 41 and 42 remain rejected under 35 USC §103 as being obvious over US Patent No. 6,126,939 to Eisenbach-Schwartz, et al. in view of US Patent No. 6,326,386 to Watson, et al. The Examiner asserts that Applicants' previous amendment of claim 2 has introduced ambiguity into the claim and, in any event, that said amendment failed to exclude the dipeptide Arg-Cys. Applicants do not agree that any ambiguity has been generated and that said ambiguity leaves the claims unpatentable in view of the cited prior art. In the interest of expediting

prosecution of the application, however, the moiety $CONR_6$ has been deleted from the definition of substituent X.

In light of this amendment, whether or not Eisenbach-Schwartz teaches the use of Arg-Cys is moot; the reference is silent with respect to the CPU inhibitors encompassed by the instantly claimed genus. The secondary Watson reference is also silent with regard to the CPU inhibitors of the instant invention. Thus, whether or not Watson teaches the use of thrombin inhibitors is also moot; the Watson reference cannot make up for the fundamental deficiency in the primary Eisenbach-Schwartz reference. This rejection should be withdrawn.

Claims 2, 4, 5, 8, 41 and 42 also remain rejected under 35 USC §103 as being obvious over the same Eisenbach-Schwartz primary reference in view of US Patent No. 6,020,510 to Franson, et al. The same basic arguments applied above are also appropriate to this rejection. Similarly, Franson is silent with respect to the CPU inhibitors of the instant invention and cannot make up for the deficiency of the primary reference; whether or not Franson discloses compounds that inhibit thrombin-induced platelet aggregation and treatment of various inflammatory conditions is moot. This rejection should thus also be withdrawn

Claims 2, 4, 5, 8, 41 and 42 also remain rejected under 35 USC §103 as being obvious over US Patent No. 4,177,277 to Ondetti, et al. in view of the same secondary reference of Watson, et al. Applicants' agent discussed this rejection with the Examiner on October 20th. The basis for rejection is not entirely clear to Applicants. However, although the Examiner was not able to clarify unequivocally that this is the case, it appears that the basis for the rejection is the contention that

the R_1-X component of instant formula I can be aminopentyl, and this is said to be homologous to the aminobutyl function possible in formula II of Ondetti. The Examiner has cited case law in support of the contention that compounds differing by a single methylene group, by definition homologous compounds, would be considered obvious variants of one another. Applicants disagree with this assessment, certainly in the present context.

Applicants note that the compounds of Ondetti formula II are intermediates in the preparation of the active Ondetti compounds. The active compounds of Ondetti differ significantly from the instantly claimed compounds, both in their structures and in their disclosed properties. Thus, the question of whether or not the aminobutyl-containing Ondetti **intermediates** might have the same properties as the instantly claimed aminopentyl-containing **active compounds** cannot, or at least should not, even arise. There are no properties per se ascribed to the Ondetti intermediates; they are simply stepping-stones in the path to production of the Ondetti active compounds, whose properties, again, are not those of the instant compounds. Thus, whether or not one can find a compound of Ondetti formula II that is homologous to a compound within the genus of instantly claimed active compounds is irrelevant to an obviousness analysis.

Furthermore, if one were to assign a value of 5 to m in Ondetti formula II, something which the Examiner has acknowledged is not taught by Ondetti, one could not even obtain the Ondetti end products from the resultant intermediates. Thus, to further address the Examiner's stated basis for leveling this rejection, there would be no motivation to increase m in Ondetti formula II based on the expectation of

obtaining compounds with similar properties (nor, for that matter, would there be motivation for any other reason). The Ondetti teaching is clear as to the desirable limits on the scope of the intermediates leading to the active end products. Any analysis with respect to homology in this particular context is inappropriate. This rejection too should be withdrawn.

The Examiner's remarks on pages 6 and 7 of the Advisory Action were also discussed on October 20th. As discussed, although these remarks were ostensibly made in connection with prior art rejections, they have the tenor more of enablement rejections. Applicants' agent understood from the Examiner during the discussion that the Examiner agrees that the claims currently being examined are enabled and that, once the remaining prior art issues are resolved, said claims would be allowable. As agreed, it may be premature at this time to get too deeply involved in analysis of such issues as enablement of the method-of-treatment claims, since no such claims are presently being considered by the Examiner. However, in anticipation of the rejoining of such claims to the allowed compound claims and in the interest of going on the record with some response to the Examiner's remarks already of record in connection with these issues, Applicants provide the following response to the Examiner's remarks in the Advisory Action.

An ongoing theme of the Examiner in the prior art rejections is the questioning of whether the unexpected results clearly shown in the instant specification for specific thrombin inhibitors in combination with CPU inhibitors could be extended to other members of the thrombin-inhibitor class "which were never contemplated by applicants, or at least which were never disclosed in the specification." To address this issue,

Applicants provided, with their last response, copies of several publications and provided an explanation of their relevance to said issue. The Examiner's reply was to state that the references "do not show 'unexpected results' that are directly relevant to the issue raised by the examiner's §103 rejections."

Applicants did not provide the references to demonstrate synergy per se with other thrombin inhibitors. The purpose was to show that inhibition of thrombin results in decreased activation of CPU, which in turn enhances clot lysis, and thus to show that this decrease of CPU activation is achieved regardless of the mechanism of action of the thrombin inhibitor. This was meant to provide support for the idea that the present scope of claim 2 is enabled, i.e., that one of skill in the art would find credible the assertion that thrombin inhibitors beyond those specifically disclosed would be similarly effective in combination with CPU inhibitors. Applicants further wish to point out to the Examiner that the disclosure on page 27, lines 6-21 of the instant specification provides ample guidance as to the nature of the thrombin inhibitors to be used in practicing the instant invention.

The Examiner has again raised the issue of unexpected results in other contexts as well. Firstly, the assertion is again made that the results presented in Tables I to III of the specification are not "unexpected" in the context of diseases which, in the Examiner's opinion, would not be candidates for treatment with a mixture of a thrombin inhibitor and a CPU inhibitor. Applicants wish to remind the Examiner, in the first place, that synergy in almost any context is unexpected. Whether or not someone outside the field, e.g., someone interested in cancer treatment, would consider the instant

results exciting or relevant to their own work is immaterial to the consideration of patentability; Applicants' results meet the criteria for unexpectedness in any event.

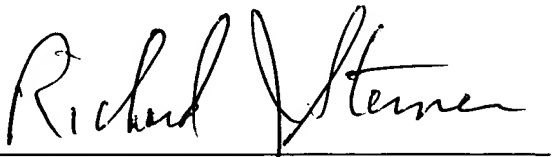
Secondly, the Examiner opines that "various uses are suggested which have little relevance to the 'unexpected results' that were obtained." The uses particularly singled out by the Examiner are the treatment of Alzheimer's disease, atherosclerosis and septic shock. As pointed out to the Examiner during the October 20th telephone discussion, there is disclosed a "nexus" that unites these and other diseases as candidates for treatment with the mixture of inhibitors that is the instant invention. Such disclosure can be found in the specification in the passage running from page 32, line 24 through page 34, line 2. Disclosure particularly relevant to those diseases cited by the Examiner can be found on page 33, lines 5-29.

Again, it is Applicants' understanding, in the wake of the discussion between their agent and the Examiner, that, upon resolution of the outstanding prior art issues, the claims currently being considered would be allowable. These issues have now been fully resolved; reconsideration and allowance of pending claims 2, 4-8, 41 and 42 are respectfully requested. It is further requested that the appropriate "kit" claims and method-of-use claims be rejoined to the composition claims and also considered by the Examiner.

The Commissioner is hereby authorized to charge any fee which may be due in connection with this communication to Deposit Account No. 23-1703.

Dated: November 5, 2004

Respectfully submitted,



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